transcriptional regulatory sequence operably linked to the coding region of a [heterologous] gene that is essential for replication of said virion, comprising culturing the isolated cell of claim 30 and recovering said virion from said cell.

C5

Remarks

I. Support for Amendments to the Claims

Support for the foregoing amendments to the claims may be found throughout the specification. Specifically, support for the amendments to claims 1, 19, 29, 30 and 40 may be found, *inter alia*, at page 6, line 25, to page 7, line 7, and at page 14, lines 1-18; and support for new claims 41 and 42, and for the amendments entering the language "isolated cell" into claims 19 and 30, may be found, *inter alia*, at page 8, line 21, to page 9, line 9, and at page 30, line 10, to page 31, line 4. Accordingly, the present amendments are not believed to add new matter.

II. Status of the Claims

New claims 41 and 42 are sought to be added by the foregoing amendments. Claims 1, 5, 10, 11, and 19-40 have been amended by the foregoing amendments, which are not believed to introduce new matter. Claims 1-42 are thus pending in the present application.

III. The Claimed Invention

The present invention relates generally to recombinant vectors, particularly recombinant adenovirus vectors. The invention specifically relates to replication-conditional vectors, particularly vectors that undergo tissue-specific replication. The vectors of the invention

preferably comprise a heterologous tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for replication of the vectors. The invention also relates to isolated cells, particularly cell lines, containing such replication-conditional vectors. The invention also relates to methods for distributing a polynucleotide *in vivo* comprising introducing such vectors into the cells or tissues of an animal. In one preferred embodiment, such methods may be used to screen a tissue for the presence or absence of transcriptional regulatory functions that permit vector replication by means of the transcriptional regulatory sequence. In another preferred embodiment, such methods may be used to provide a therapeutic benefit from the presence of the vector *per se* or from heterologous gene products expressed from the vector and distributed throughout cells tissues into which the vectors have been introduced. The present invention thus provides compositions and methods, not previously available in the art, that may be used for a variety of clinical and diagnostic purposes.

IV. Summary of the Office Action

In the Office Action dated July 21, 1997, the Examiner has made one objection to, and six rejections of, the claims. Applicants respectfully offer the following remarks to overcome or traverse each of these elements of the Office Action, in light of the above amendments.

V. The Objection to the Amendment Filed April 17, 1997, is Overcome

In the Office Action at page 2, the Examiner has objected to the amendment filed April 17, 1997 (Paper No. 14) under 35 U.S.C. § 132 because it allegedly introduces new matter into the disclosure. Specifically, the Examiner contends that the phrase "a heterologous gene

essential for replication" as recited in claims 1, 19, 29, 30, and 40 is not supported by the original disclosure. Applicants note that the amendment to claim 30 sought to be entered in the amendment filed April 17, 1997, has not been entered by the Examiner (*see* Office Action at page 2, lines 2-4). Therefore, claim 30 as presented prior to the foregoing amendment did not, and now still does not, recite the phrase "a heterologous gene essential for replication." By the foregoing amendments, Applicants have deleted the term "heterologous" preceding the term "gene" in each of claims 1, 19, 29 and 40, and have amended these claims and claim 30 to recite the phrase "a heterologous tissue-specific transcriptional regulatory sequence" which is fully supported by the specification as originally filed. Therefore, Applicants respectfully assert that the Examiner's objection has been fully accommodated, the foregoing amendments do not introduce new matter, and the present application is thus in compliance with 35 U.S.C. § 132.

VI. The Rejection of Claims 1-40 under 35 U.S.C. § 112, First Paragraph, is Traversed

In the Office Action at pages 2-10, the Examiner has rejected claims 1-40 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants had possession of the claimed invention at the time the application was filed. Applicants respectfully traverse this rejection, in view of the foregoing amendments and the following remarks.

In making this rejection, the Examiner first contends

> The phrase "a heterologous gene essential for replication of said vector" as recited in claim 1, line 3, for example, is not properly described in the application as filed because it is not apparent as to how said term is described in the disclosure of the application . . . . Since the application does not provide any guidance to the artisan on how to employ a heterologous gene essential for replication of the claimed vector, said gene is under the control of a heterologous tissue-specific promoter, it is not apparent as to

how the artisan can practice the claimed invention without undue experimentation.

Office Action at page 3, lines 1-3 and lines 9-12. As noted above, by the foregoing amendments, Applicants have deleted the term "heterologous" preceding the term "gene" in each of claims 1, 19, 29 and 40, and have amended these claims and claim 30 to recite the phrase "a heterologous tissue-specific transcriptional regulatory sequence." This language is fully supported and enabled by the specification as originally filed, as acknowledged by the Examiner's statement at page 6, lines 10-11 of the Office Action that "the specification is enabled for original claims directed to expression vectors and methods of making the vectors". Therefore, this portion of the Examiner's objection has been fully accommodated, and claims 1-8 and 19-40 as amended are free of the rejection under 35 U.S.C. § 112, first paragraph.

The Examiner also contends that claims 9-18, which are directed to a method of distributing a polynucleotide in a tissue *in vivo* using the claimed vectors, "encompass gene-targeted therapy in any subject including a human." Office Action at sentence bridging pages 3-4. The Examiner further contends that such gene-targeted therapy methods are unpredictable and that "without guidance from the specification the artisan would have been required [to] practice undue experimentation to construct and use the claimed vectors." Office Action at page 5, lines 7-8. The Examiner relies on the comments of Crystal, Coglan, Gunzburg, Mastrangelo, Ledley, Dillon, Pennisi, and Orkin and Motulsky, to support the contention that targeted gene therapy remains unpredictable. Applicants respectfully disagree with these contentions as they are applied to the invention as presently claimed.

Undue experimentation is a conclusion that is reached by weighing many factual considerations. These considerations have been enumerated in *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. Int. 1986), and include (1) the quantity of experimentation necessary, (2) the

amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Under *Forman*, a determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness having due regard for the nature of the invention and the state of the art. The test is not merely quantitative since a considerable amount of experimentation is permissible, if routine or if the specification in question provides sufficient guidance with respect to the direction in which the experimentation should proceed in order to enable one of ordinary skill in the art to practice the claimed invention. The emphasis is not on the term "experimentation" but on the term "undue". *See In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Applicants respectfully submit that the present rejection of claims 9-18 has been based entirely on consideration of only one of the *Forman* factors: the predictability factor. Further, Applicants respectfully submit that insufficient evidence has been offered to support the conclusion that the invention is sufficiently unpredictable that it is not enabled to any degree. Accordingly, as discussed below, Applicants respectfully disagree with the rationale for the rejection and submit that a *prima facie* case of nonenablement has not been established.

These above-noted comments by Crystal, Coglan, Gunzburg, Mastrangelo, Ledley, Dillon, Pennisi, and Orkin and Motulsky simply indicate that there was no *clinical* evidence, as of the date of filing of the present application, that genetic treatment has produced therapeutic benefits. There is simply no reason for the overextension of this opinion, as the Examiner has apparently done, to support the assertion that the present methods could not be used by the skilled artisan without undue experimentation. In making these contentions, the Examiner appears to suggest

that for the claimed invention to be enabled, Applicants must demonstrate the clinical efficacy of the claimed methods (*i.e.*, that the methods are without obstacles, are safe, and are therapeutically effective) in order to overcome the outstanding enablement rejection. Applicants wish to remind the Examiner, however, that there is no requirement for clinical data to prove that an application is in compliance with 35 U.S.C. § 112, first paragraph. In fact, description of *in vitro* and/or animal testing has been held to enable claims to *in vivo* therapeutic compositions and methods of their use. To this end, the Federal Circuit has stated that:

> In vitro testing, in general, is relatively less complex, less time consuming, and less expensive than in vivo testing. Moreover, in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

Cross v. Iizuka, 753 F.2d 1040, 1050 (Fed. Cir. 1985); *see also In re Brana*, 51 F.3d 1560, 1567-68 (Fed. Cir. 1995) (holding that animal testing results are sufficient to establish whether one skilled in the art would believe that a pharmaceutical compound has an asserted clinical utility for the purposes of compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph). The present specification clearly describes methods for preparation and use of the present vectors *in vitro, in vivo* and *ex vivo* (*see, e.g.*, Specification at pages 21-32). Under *Cross* and *Brana*, one of ordinary skill would thus recognize that the *in vitro* assays described in the present specification would be "generally predictive of *in vivo* test results", *Cross*, 753 F.2d at 1050, and thus would have a reasonable expectation that the claimed methods would be successful for the claimed *in vivo* therapeutic approaches.

Additionally, the Examiner's contentions that "the claims encompass gene-targeted therapy," and that gene therapy allegedly remains unpredictable, are not relevant to enablement

of the present claims. While Applicants teach that the presently claimed invention is operable *in vivo*, claims 9-18 do not specifically recite *in vivo* therapeutic efficacy but instead recite the distribution of a polynucleotide in a tissue *in vivo*. Applicants wish to remind the Examiner that there are other uses for such a process which are *unrelated* to therapy, including but not limited to the production of a cell line that produces large amounts of the present vectors. It is improper for the Examiner to reject the claims based on the possibility of allegedly inoperable embodiments, since it is not a function of the claims to specifically exclude possible inoperative embodiments. The mere hypothetical possibility that a method claim may embrace an inoperable process step or utility does not *per se* render the claim non-enabled.

The nature of the present invention alone would not cause one skilled in the art to reasonably doubt the asserted usefulness. The purpose of delivering nucleic acids to cells or tissues using the claimed methods, vectors and compositions does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. One skilled in the art would be without basis to reasonably doubt Applicants' asserted utility on its face, and Applicants should not be required to substantiate their presumptively correct disclosure to overcome the present rejection under 35 U.S.C. § 112, first paragraph. Additionally, according to the "Guidelines for Examination of Applications for Compliance with the Utility Requirement," issued by the Honorable Commissioner of Patents and Trademarks, "[i]f the applicant has asserted that the claimed invention is useful for any particular purpose and that assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on § 101." *See Guidelines for Examination of Applications for Compliance with the Utility Requirement*, at Part I, Section B(2)(a), 1170 OG at 460-461 (January 24, 1995). Although the present Guidelines are specific to § 101 rejections, they are also to be applied to § 112, first

paragraph, rejections. *See Brana*, 51 F.3d at 1564. Accordingly, under *Brana* and the Utility Guidelines, Applicants submit that claims 9-18 encompassing the potential use of, or methods involving, *in vitro* and *in vivo* applications of the claimed vectors are fully enabled by the present and original specification.

Furthermore, at the time the invention was made, ample information was available to skilled artisans regarding various ways of "whole animal" treatment with transfection vectors carrying a gene of interest. It is not relevant to the inquiry at hand, *i.e.*, to the "patentability" of the claimed invention, that certain investigators (such as those relied upon by the Examiner above) were not satisfied with the level of efficacy and safety of gene therapy at the *clinical* level. It is an incorrect application of patent law for the Examiner to require Applicants to demonstrate routine, highly effective, and safe methods of gene therapy to support enablement of a claim to methods of using the claimed vectors to distribute a polynucleotide in a tissue *in vivo*. It is sufficient for patentability purposes that the invention can be practiced *at all* as taught in the specification and in light of the knowledge in the art. Whether the invention would meet agency standards for routine medical application is an inquiry specifically reserved for the Food and Drug Administration, and is irrelevant to patentability. *See Brana*, 51 F.3d at 1567.

Applicants respectfully assert that the art is replete with various examples of successful transfection of nucleic acid molecules *in vivo*. The Examiner does not dispute that various gene therapy methods were known in the art at the filing date of the application; indeed, the Examiner acknowledges as much by citing Huber, Scott and Stratford-Perricaudet in the rejections under 35 U.S.C. §§ 102 and 103 above. Hence, it would be clear to the skilled artisan that the same types of transfections may now be done using the vectors, compositions and methods of the present invention to increase gene expression in cells and tissues *in vivo*, according to an

embodiment of the claimed invention. Whether further research and development, however, would be required to perfect the available gene therapy methods is not material to the patentability of the claimed invention. It is, in fact, expected that such improvements to most inventions are required in order to develop a safe and desirable invention for routine use. In view of the foregoing remarks, Applicants therefore respectfully assert that claims 9-18 are fully enabled by the present specification, and that one of ordinary skill would not be required to undertake undue experimentation to make and use the invention as claimed.

Finally, in making this rejection the Examiner contends

> While the specification is enabled for original claims directed to expression vectors and methods of making the vectors, the specification is not enabled for claims directed to cells containing the claimed vectors, and to methods for distributing a polynucleotide *in vivo*, since claims directed to cells and methods of use do encompass targeted gene therapy wherein a therapeutic response is generated in any subject, particularly given the reasons set forth in this Office action, and given the Dillon, Orkin and Motulsky, Pennisi, Crystal, Coghlan, Gunzburg *et al.*, Mastrangelo *et al.*, and the Ledley references indicating that targeted gene therapy remains unpredictable.

Office Action at page 6, lines 10-19. By the foregoing amendments, Applicants have amended claims 19-40 to recite an *isolated* cell containing a vector such as that of claim 1. One of ordinary skill would recognize that an isolated cell does not refer to a cell *in vivo*. Thus, the Examiner's contentions regarding the alleged unpredictability of gene therapy methods and distribution of polynucleotides *in vivo* are not germaine to the isolated cell of amended claims 19-40.

Accordingly, Applicants respectfully assert that, contrary to the Examiner's contentions, the present specification fully discloses and enables the subject matter of claims 1-40 in such a way as to convey to one of ordinary skill that Applicants had possession of the claimed invention at

the time of filing of the present application. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are therefore respectfully requested.

VII. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Are Traversed

In the Office Action at pages 10-11, the Examiner has rejected claims 1-40 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner contends that claims 1-8 and 19-40 are indefinite in the recitation of the term "capable of." Applicants respectfully disagree with these contentions. The present specification amply indicates that the vectors of the invention undergo replication in certain cells under certain conditions. *See, e.g.*, specification at pages 6-7, at page 14, and at pages 22-23. Specifically, by containing a gene essential for vector replication operably linked to a tissue-specific regulatory sequence the present vectors will undergo replication within a target cell only when the regulatory sequence has been activated or derepressed. Thus, the vectors of the invention are replication-*competent* (*i.e.*, they are "capable" of replicating), but they are also replication-*conditional* (*i.e.*, they are capable of replicating in certain cells only under conditions where the regulatory sequence is activated or derepressed). Therefore, one of ordinary skill would understand what is meant by a vector that is "capable of tissue-specific replication" -- *i.e.*, a vector that retains the ability to replicate in certain cells under certain conditions, or a "replication-conditional" vector that is "replication-competent" in certain cells under appropriate conditions. A vector that is "capable" of replication would thus be understood by one of ordinary skill to mean the converse of a "replication-deficient" or "replication -defective" vector (as those

terms are also understood in the art) which has been treated or has mutated such that it no longer can undergo replication under *any* conditions.

However, solely to expedite prosecution, Applicants have now amended independent claims 1, 19, 29, 30 and 40 to delete the phrase "capable of tissue-specific replication" and to indicate that the vector of the invention is replication-conditional and undergoes tissue-specific replication. As indicated above, these amendments are fully supported in the specification as originally filed. Therefore, Applicants respectfully assert that this portion of the rejection has been overcome by the foregoing amendments and remarks.

The Examiner also contends that claims 1-8, 19-29 and 40 are indefinite in the recitation of "a heterologous gene essential for replication." By the foregoing amendments, Applicants have deleted the term "heterologous" preceding the term "gene" in each of claims 1, 19, 29 and 40, and have amended these claims and claim 30 to recite the phrase "a heterologous tissue-specific transcriptional regulatory sequence" which is fully supported by the specification as originally filed. Therefore, Applicants respectfully assert that this portion of the rejection has been overcome by the foregoing amendments.

The Examiner also contends that claim 5 is vague and indefinite in referring to the "method" of claim 4, since claim 4 is not directed to a method. By the foregoing amendments, Applicants have amended claim 5 to refer to the *vector* to which claim 4 is directed. Therefore, Applicants respectfully assert that this portion of the rejection has been overcome by the foregoing amendments.

The Examiner also contends that claims 10 and 11 are vague and indefinite in referring to the "vector" of claim 9, since claim 9 is directed instead to a method. By the foregoing amendments, Applicants have amended claims 10 and 11 to refer to the *method* to which claim 9

is directed. Therefore, Applicants respectfully assert that this portion of the rejection has been overcome by the foregoing amendments.

The Examiner also contends that claims 19-28 and 30-39 are indefinite in the recitation of "a cell" since it is not apparent whether the cell is directed to an isolated cell or an implanted cell *in vivo*. By the foregoing amendments, Applicants have amended claims 19 and 30 to recite "an isolated cell" which is supported in the specification (*see, e.g.*, pages 8-9 and 28-31). Therefore, Applicants respectfully assert that this portion of the rejection has been overcome by the foregoing amendments.

In view of the foregoing amendments and remarks, Applicants respectfully assert that claims 1-40 particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Reconsideration and withdrawal of the rejection of claims 1-40 under 35 U.S.C. § 112, second paragraph, are therefore respectfully requested.

VIII. The Rejection of Claims 9-12, 17 and 18 under 35 U.S.C. § 102(b) Is Traversed

In the Office Action, the Examiner has rejected claims 9-12, 17 and 18 under 35 U.S.C. § 102(b) as being anticipated by Huber *et al.* (EP 0 415 731 A3; hereinafter "Huber"). In making this rejection, the Examiner contends

> Huber *et al.* disclose a method for distributing a thymidine kinase gene in a specific tissue, *e.g.*, cancerous tissue, comprising the use of a retroviral vector, wherein said vector comprise [sic] a 5' and 3' viral LTR sequence operably linked to a heterologous tissue specific regulatory sequence (p. 3 and 6). More specifically, the disclosed regulatory sequences of Huber *et al.* is [sic] alpha-fetoprotein, CEA, HER-2/neu, and tyrosine hydroxylase transcriptional regulatory sequence (p. 4).
>
> Absent evidence to the contrary, the method of Huber *et al.* has all the properties cited in the claims.

Office Action at page 11, lines 5-12. Applicants respectfully disagree with these contentions, based on the foregoing amendments and the following remarks.

As noted above, the methods and compositions of the present invention are based on vectors that are replication-conditional, that is, they are replication-competent in certain cells under certain conditions. The vectors of the present invention have three essential elements, as fully described in the specification and as specified in claim 9: a.) a heterologous tissue-specific regulatory sequence; b.) a gene essential for vector replication operably linked to the regulatory sequence; and c.) the ability to undergo replication in a cell or tissue when the regulatory sequence is activated or derepressed. Thus, it important to recognize that the present vectors are replication-*competent*, not replication-*deficient*.

The vectors and methods of Huber do not anticipate those of the present invention. The retroviral vectors described by Huber have had the retroviral *gag*, *pol* and *env* genes removed (*see* Huber at page 6, lines 6 and 45). As one of ordinary skill would appreciate, and as Huber indicates at page 6, line 57, the vectors provided by Huber are replication-*deficient*. Furthermore, in the Huber vectors, the gene that is operably linked to the regulatory sequence encodes a heterologous enzyme (*see* Huber at page 5, line 8) such as thymidine kinase, rather than being a gene essential for replication of the vector as in the present invention. Therefore, contrary to those of the present invention, the vectors of Huber are missing a gene essential for vector replication and are *not* replication-competent. Since the vectors of Huber lack at least two key elements of the vectors of claim 9, and thus of claims 10-12, 17 and 18 which depend therefrom, Huber cannot and does not anticipate claims 9-12, 17 and 18. The rejection on these grounds is therefore in error and should be withdrawn.

Based on the foregoing remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 9-12, 17 and 18 under 35 U.S.C. 102(b).

IX. The Rejection of Rejection of Claims 1, 2, 4, 5, 8-10, 12-14, 17-20, 22-24, 27-31, 33-35 and 38-40 under 35 U.S.C. § 102(b) Is Traversed

In the Office Action at pages 11-12, the Examiner has rejected 1, 2, 4, 5, 8-10, 12-14, 17-20, 22-24, 27-31, 33-35 and 38-40 under 35 U.S.C. § 102(b) as being anticipated by Scott *et al.* (WO 93/09239; hereinafter "Scott"). In making this rejection, the Examiner contends

> Scott *et al.* disclose hybrid parvovirus vectors, methods of producing and using said vectors (entire document). The hybrid parvovirus vectors which comprise a pair of AAV inverted terminal repeats (ITRs) which flank at least one cassette containing the p6 promoter of B19 parvovirus which directs cell-specific expression operably linked to a heterologous gene, *e.g.*, MDR gene or TNF gene (p. 9 bridginng [sic] p. 10, pp. 13 and 14). More specifically, Scott *et al.* disclose the use of a transcriptional promoter of B19 to effect tissue-specific expression of heterologous sequences (p. 11). Methods of constructing and producing vectors and virions are disclosed in Examples 1-5. Absent evidence to the contrary, the Scott *et al.* [sic; reference] has all the properties cited in the claims.

Office Action at page 11, line 15, to page 12, line 4. Applicants respectfully disagree with these contentions, based on the foregoing amendments and the following remarks.

As noted above, the vectors presently described and claimed are replication-competent in certain cells, and contain a gene essential for vector replication operably linked to a heterologous tissue-specific regulatory sequence. As was the case for the disclosure of Huber noted above, the disclosure of Scott does not anticipate the present claims. The parvovirus vectors of Scott have been manipulated to be replication-*deficient*. As noted in Scott at page 10, lines 7-10, ". . . the portions of the DNA responsible for replication of the parvovirus have been deleted, and therefore these vectors cannot self replicate." Furthermore, the regulatory sequence contained in the Scott

vectors is *not* heterologous but is derived from the parvovirus genome, while the gene operably linked to the virus regulatory sequence *is* heterologous (*see* Scott at page 9, lines 19-30). Finally, the gene operably linked to the regulatory sequence in the vectors of Scott is not essential for viral replication, but is instead a "biologically functional protein" such as "a protein which is essential for normal growth of the cell or for maintaining the health of a mammal" (*see* Scott at page 12, lines 25-31). Therefore, the vectors of Scott are a) replication-deficient, b) contain a non-heterologous regulatory sequence which is operably linked to c) a gene that is not essential for replication of the vector. The Scott vectors therefore are substantially different from those of the present invention and thus, Scott cannot and does not anticipate claims 1, 2, 4, 5, 8-10, 12-14, 17-20, 22-24, 27-31, 33-35 and 38-40. The rejection on these grounds is therefore in error and should be withdrawn.

Based on the foregoing remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1, 2, 4, 5, 8-10, 12-14, 17-20, 22-24, 27-31, 33-35 and 38-40 under 35 U.S.C. 102(b).

X. The Rejection of Rejection of Claims 1, 2, 4-10, 13-20, 22-27, 29-31 and 33-40 under 35 U.S.C. § 102(b) Is Traversed

In the Office Action at page 12, the Examiner has rejected claims 1, 2, 4-10, 13-20, 22-27, 29-31 and 33-40 under 35 U.S.C. § 102(b) as being anticipated by Stratford-Perricaudet *et al.*, *Human Gene Transfer 219*:51-61 (1991) (hereinafter "Stratford-Perricaudet"). In making this rejection, the Examiner contends

> Stratford-Perricaudet *et al.* disclose a method of producing adenoviral vectors for targeted gene therapy, *e.g.* targeting neurons *in vivo*, (entire document). Said vector comprises the ITR sequences, and packaging sequences from the AD5 genome (essential for replication) operably linked to the MLP/TPL from

> the AD2 genome (*e.g.*, which is essential for the transcription for late viral transcripts) followed by a heterologous gene and the E4 gene region which encodes a number of proteins that are involved in the regulation of late gene expression and in the shutoff of host protein synthesis (Fig. 2). Thus, the vectors of Stratford-Perricaudet *et al.* comprise the ITR and packaging sequences heterologous to the MLP/TPL regulatory sequence which also is essential for replication of the vectors, and absent evident [sic] to the contrary the vectors have all the propertices [sic] cited in the claims.

Office Action at page 12, lines 7-16. Applicants respectfully disagree with these contentions, based on the foregoing amendments and the following remarks.

As noted above, the vectors presently described and claimed are replication-competent, and contain a gene essential for vector replication operably linked to a heterologous tissue-specific regulatory sequence. As was the case for the disclosures of Huber and Scott noted above, the disclosure of Stratford-Perricaudet does not anticipate the present claims.

The adenovirus vectors of Stratford-Perricaudet have been manipulated to be replication-*deficient*. In the legend to Figure 3 at page 55, it is indicated that the vectors of Stratford-Perricaudet were prepared "by replacing the internal E1 region of adenovirus by foreign sequences . . . ." As one of ordinary skill would appreciate, since the E1a region of the adenovirus has been deleted, the vectors prepared and used in Stratford-Perricaudet are replication-deficient. Indeed, Stratford-Perricaudet indicates this very fact by stating throughout the paper that the vectors are replication-deficient: the vectors are dramatically impaired in replication (*see* page 54, third paragraph); there is an "absence of efficient viral replication" in the vectors (*Id.*); the goal of the studies in Stratford-Perricaudet was "to assess the degree of effectiveness of replication-deficient adenoviruses," (*see* page 56, second full paragraph); and, as the Examiner has acknowledged in the Office Action at page 13, lines 4-5, the vectors of Stratford-Perricaudet are "an attractive gene transfer system" because they may be used "to

express a gene in the absence of both viral and cellular replication . . . " (*see* Abstract at page 51). Thus, the vectors of Stratford-Perricaudet have had the gene(s) essential for replication of the virus deleted, rather than being operably linked to any promoter, let alone a heterologous and/or tissue-specific promoter. Furthermore, contrary to the Examiner's contention, the ITR and packaging sequences were not *operably* linked to a promoter in Stratford-Perricaudet; these sequences are simply structural and their expression cannot therefore be regulated by any promoter sequence. In addition, Stratford-Perricaudet only describes the operable linkage of a gene for a biological protein (*e.g.*, HBsAg) to a promoter, rather than operably linking a gene essential for vector replication to the promoter. Finally, the replacement of the Ad5 MLP promoter with the Ad2 MLP promoter in Stratford-Perricaudet is simply the exchange of a promoter from one adenovirus serotype for that of another adenovirus serotype. Since the level of nucleotide homology between Ad5 and Ad2 approaches 90-100%, such an operation would not be recognized by one of ordinary skill as replacing the adenovirus promoter with a "heterologous" promoter as one of ordinary skill would understand that term to be defined (and as is defined in the specification at page 13).

Therefore, like those of Scott, the vectors of Stratford-Perricaudet are a) replication-deficient, b) contain a non-heterologous regulatory sequence which is operably linked to c) a gene that is not essential for replication of the vector. The Stratford-Perricaudet vectors therefore are substantially different from those of the present invention and thus, Stratford-Perricaudet cannot and does not anticipate claims 1, 2, 4-10, 13-20, 22-27, 29-31 and 33-40. The rejection on these grounds is therefore in error and should be withdrawn.

Based on the foregoing remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(b) over Stratford-Perricaudet.

XI. The Rejection of Rejection of Claims 3, 11, 12, 21, 28 and 32 under 35 U.S.C. § 103 Is Traversed

In the Office Action at pages 12-13, the Examiner has rejected claims 3, 11, 12, 21, 28 and 32 under 35 U.S.C. § 103 as being unpatentable over Stratford-Perricaudet and Huber. In making this rejection, the Examiner contends

> Stratford-Perricaudet *et al.* is applied here as indicated above. Furthermore, Stratford-Perricaudet *et al.* disclose that "because adenovirus is capable of infecting a wide variety of cell types in culture, it may prove realistic to use such a vector to target any organ *in vivo*["] (p. 58), and that "the potential of this virus to accommodate a large piece of DNA and to express a gene in the absence of both viral and cellular replication make this virus an attractive gene transfer system" (p. 51, abstract).
>
> Huber *et al.* teach the use of tissue-specific promoters for targeting toxic genes to cancerous cells. The disclosed regulatory sequences of Huber *et al.* is [sic] alpha-fetoprotein, CEA, HER-2/neu, and tyrosine hydroxylase transcriptional regulatory sequences (p. 4).
>
> It would have been obvious for one of ordinary skill in the art at the time the invention was made to have modified the adenoviral vectors of Stratford-Perricaudet *et al.* by employing any of the tissue-specific promoters disclosed in Huber *et al.* to specifically target therapeutic gene [sic] to a tumor site, given the teaching of Stratford-Perricaudet *et al.* indicating the advantage of using adenoviral vectors as an expression vector for gene transfer protocols, and given the teaching of Huber *et al.* disclosing that by using expression vectors comprising a tissue specific promoter operably linked to a toxic gene *in vivo*, the vectors are effective for delivering the toxic gene to a target tissue for expression.
>
> Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Office Action at page 13, lines 1-19. Applicants respectfully disagree with these contentions, based on the foregoing amendments and remarks, and further in view of the following additional remarks.

As noted above, the present invention is directed to replication-conditional (*i.e.*, replication-*competent*) vectors and methods and compositions using these vectors. As also noted

above, both Stratford-Perricaudet and Huber disclose only replication-*deficient* vectors. Therefore, contrary to the Examiner's contentions, the disclosures of Stratford-Perricaudet and Huber actually teach *away* from the present vectors, compositions and methods. Indeed, the Examiner acknowledges this fact in stating, as noted above, that the vectors of Stratford-Perricaudet may be useful because they operate in the *absence of viral replication*. There is no suggestion, implication or contemplation in the disclosures of Stratford-Perricaudet or Huber that the methods disclosed in those references, alone or in combination, could be used to produce the vectors, methods and compositions of the present invention which rely on replication-competent vectors. Therefore, one of ordinary skill would not be motivated to make and use the vectors, methods and compositions of the present invention based solely on the disclosures of Stratford-Perricaudet and Huber. Absent such suggestion and motivation, Stratford-Perricaudet and Huber cannot be properly combined to establish a *prima facie* case of obviousness. *See In re Fine*, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988). Applicants therefore respectfully assert that claims 3, 11, 12, 21, 28 and 32 would not have been obvious to one of ordinary skill over Stratford-Perricaudet and Huber.

In view of the foregoing amendments and remarks, Applicants respectfully assert that a *prima facie* case of obviousness of claims 3, 11, 12, 21, 28 and 32 has not been established. Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 are respectfully requested.

XII. Summary

All of the Examiner's grounds for rejection of the claims have been properly traversed, accommodated or rendered moot by the above amendments and remarks. Applicants therefore

respectfully request that the Examiner reconsider and withdraw the outstanding rejections and move the application to allowance of all pending claims.

Respectfully submitted,

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